Development of sleep-disordered-breathing and obstructive sleep apnea

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Breathing

- It is a **complex function** and it involves different anatomic regions: such as:
- Nose
- Mouth
- Chest
- Abdomen
- It is controls by different parts of the brain, but particularly the brain-stem and cortical regions of the brain
- By 12 months of age, the way we normally breath is well established

Physiology of UA

- The Pharynx is a **Collapsible Tube**
- Unlike lower airways, no rigid support
- UA skeletal muscles and soft tissues support non-respiratory functions: sucking, swallowing, vocalization/ phonation, etc
- Sleep causes fundamental modifications of pharyngeal muscle **tone and reflex responses and** can can lead to narrowing and *increased upper airway resistance in normal individuals*
- *Slide-4*

Upper Airway-UA

- The physic laws that regulate the air flow in the UA are those applied in the Physics of **Fluid-Dynamics**
- **The airway is similar to a river and a river-gorge:**
- A local narrowing in compliant segments promotes further narrowing
- (this is related to the Bernoulli effect:. Acceleration of airflow at narrow segment implies: increased kinetic energy (*velocity*) and decreased potential energy (*pressure*)
- and there are more changes with creation of "eddies" as in a narrow river gorge
- **Any modification of flow will participate to collapse,**

Slide 6-7

Intrinsic Collapsibility

- UA can be modelled as a collapsible tube with **maximum flow** Vmax determined by **upstream nasal pressure (Pn)** and **Resistance** (Rn)
- The tube collapses and airflow stops at the **critical pressure called :**Pcrit.

Vmax = (P*n*-Pcrit)/R*n*

- "upstream" = nasal (n)
- Pn: nasal pressure
- Rn: nasal resistance
- Vmax: **maximum air-flow**
- **Increases in nasal pressure** will increase Vmax in the UA. (Linear relationship) (CPAP)
- **Decreases in Rn** will increases Vmax. (Surgery/weight loss)
- **Pcrit**:"critical pressure" is when the UA collapse

Pcrit varies among individuals

- Normal subjects should have a Pcrit substantially **below atmospheric pressure**
- Experimentally, normal subjects treated with subatmospheric nasal pressure develop OSA!
- **1) During expiration** the UA is submitted to sub-atmospheric pressure in normal subjects

Pharyngeal Muscle Activity is Important for Airway Patency

- **Maintaining an open UA depends**
- **+ on intrinsic collapsibility** (Pcrit)
- + and **level of pharyngeal muscle activity** that ***stiffens and enlarges*** the airway
- **During sleep muscle activity decreases:**
- **Sleep favors UA collapse due to decrease in muscle activity**
- physiologically **REM sleep associated with the largest amount of inhibition on volitional muscle tone**
- **Intrinsic** Factors
- Size: "Small airway" (lung) at end expiration **increases demand on UA muscles** to maintain patency and airflow during inspiration
- This is a tonic, reflex activation
- This compensation is lost during sleep
- **Sleep favors UA collapse due to loss of tonic activation of UA muscles at end expiration**
- Collapse of UA
- **position**:

- usually sleep occurs in a recumbent position
- the degree of recumbence has an impact on size of UA with flat on back been position leading to the largest amount of change compared to erect position:
- action of gravity and atmospheric pressure

Extrinsic Factors

- They are **non-sleep related:** extrinsic factors
- **External factors** impact on size of UA particularly when located retropalatal and retroglossal
    - **These external factors can be influenced by genetic and environmental factors**
- **Three external factors are prominent**:
    - Fat deposits (related to body-mass-index-BMI-)
    - craniofacial features (related to genetic and functional factors),
    - hypertrophied tissues (related to inflammation)

The obesity epidemic (1990s....)

- The obesity epidemic has had an impact on frequency of abnormal breathing during sleep
- Fat infiltrate:
- Tongue
- Neck
- Abdomen: there is always a degree of chest-bellow impairment and **obesity is a co-morbidity**
- When investigating an obese individual the question is : **how much of the SDB** and its co-morbidities are related directly to obesity and not to SDB: a question difficult to respond to as usually obesity has been present for years...
- It is not a pure OSA and obese patients should be consider as a problem on their own
- The **extrinsic** factors
- Fat is only a moderate factor
- **They are other factors that are present much before fat deposit**
- **And on which we may be able to act upon**
- *We may be able to recognize these factors early*
- ***SO***
- It is important to know what these extrinsic factors act upon to lead to small UA
- The search for what is the intermediary between the extrinsic factors...
- ..... and what lead to change in the UA

- Upper airway muscles appear important to have a *non-collapsible airway* when we sleep
- How do we know that?
- +Monkey studies: The role on Craniofacial Growth
- The Harvold et al Rhesus Monkey Experiments (24 monkeys) [1972-1980]
- Placement of soft hollow cone shaped silicon plugs – 10 mm long filling the nares – held in position by silk ligature nasal septum – versus normal controls.
- Consequences: **Great increase in nasal inspiratory resistance**, persistence of some expiratory flow.
- EMG study (monkey experiment)
- Systematic recording of different muscles, more particularly the geniohyoid, the genioglossal muscles
- **EMG changes** were abrupt **induction of rhythmic discharge patterns,** contrary to normal firing, near continuous and desynchronized.
- **Tonic EMG discharges changed back to the normal pattern when nasal breathing was restored** at the end of the 6-month experiment.
- Consequences (2)
- **Increase in nasal resistance** has a dramatic effect on the maxillo-mandibular skeleton: there is **halt in growth.**
- **Adaptive changes in soft tissues occur** that are associated with **deviation in jaw posture and tongue activity.**
- The nasal obstruction induces **functional changes in the naso-maxillary complex and on the mandible.**
- Summary
- In growing animals in which the nasal airway is gradually occluded, there is an **adverse effect on morphology of**:
- The **naso-maxillary complex, mandible, and pharyngeal airway** space.
- The **morphometric changes** are induced by altered functioning of the muscles, with changes in muscles firing that are **triggered by abnormal nasal resistance**
- The study was both aimed at the UA and orthodontic changes and no sleep study was performed
- BUT the study showed that abnormal nasal resistance led to **change of UA muscle activity**
- **..... that had an impact on orofacial growth**
- Systematic studies in man
- What happens if there is a dysfunction of orofacial muscle activity in human?
- As the monkey study was done om newborn monkey

- the dysfunction may be present early in life...
- Question: in human early in life **what gives muscle dysfunction?**
- \+ Genetic muscle disease
- \+ neuro-muscular dysfunction (cerebral palsy)
- *What did Neuro-muscular diseases investigation taught us on OSAS*
- Example study on Myotonic Dystrophy
- They are
- \+ associated with **abnormal EMG including in the tongue EMG**
- *+ induces obstructive sleep-disordered-breathing in children and not only a decrease in ventilation*
- *+is associated with important* ***changes in facial development*** *with* ***narrow-face and high and narrow hard palate*** (Guilleminault et al 1984)
- the OSA syndrome noted get worse with aging from childhood to adulthood
- Conclusion:
- **Abnormal muscle tone** due to genetic dysfunction
- +Does not allow normal oral facial growth
- +Lead to development of abnormal breathing during sleep
- with presence of obstructive breathing
- +The problem become *more obvious with aging*
- *+ But the muscle defect is present at birth*
- Decrease in muscle tone
- A "natural" human model:
- **The premature infant**
- Investigation of infants with abnormal muscle tone (b):
- Premature cohort
- Rationale: premature infants often present **generalized hypotonia**
- **hypotonia is noted more often when prematurity is more pronounced**
- **study:**292 premature.
- All infants had clinical evaluation, anatomic evaluation with systematic photo of the mouth and palate; questionnaires on sleep-wake development, evaluation of neuro- behavioral development-including

psychometric testing; and **actigraphy and systematic PSG during 1st week after birth**

- **Follow-up** at 3, 6 12 ,24 and 36 months
- **Outcome**
- **Subgroup B n=230 (evolution as expected)**
- Infants between 27 and 35 GA, all kept in hospital post delivery but none had intubation or tubing
- All had generalized hypotonia of prematurity, younger GA more affected, presence of" apnea of prematurity" in n=207
- Presence of high palate and low place tongue: 100% palatal width calculated at mean 14mm
- Follow-up at 3 months
- *Presence of central, mixed and obstructive apnea with mouth breathing n=230,*
- *presence of high and narrow hard palate: 100%*
- *Presence of low place tongue :100%*
- *Follow-up at 6 months*
- Daytime mouth breathing: 100% with high and narrow hard palate and low place tongue and visually small upper airway
- Absence of enlarged tonsils
- Rare snoring
- PSG: obstructive and mixed sleep apneas and hypopneas: (AHI>1 with mouth breathing) ;100%
- **Slides33-36**
- **Follow-up of premature infants from birth to 4 years of age**
- ***77% at 4 years have OSA*, particularly those born at 36 weeks or younger**
- **They had hypotonia at birth**
- **……. They have a small mouth at 4 years**

- **They did not grow well their orofacial structures between birth and 4 years of age**

What is normal at birth?

- **An infant that can**
-
- **+breath through is nose [human=obligatory nose breather]**

+ suck, feed on breath milk and swallow without difficulties

We know : at birth *normal humans have*

- Mouth and throat structures in very close proximity
- Limited open space within mouth and throat areas
- A small, slightly retruded (pulled back) lower jaw
- A wide "U" shaped palate
- A flexible/moveable palate
- Nose breathing
- A tongue that fills the mouth at rest
- A deeply cupped tongue when suckling
- Gums that enlarge to assist with the latch
- Ample sucking pads in the cheeks
- Relatively horizontal positioning of the Eustachian tubes
- . There is significant jaw growth in the first year of life
- At birth anatomy aims at appropriate sucking with nasal breathing

Why premature infants are more at risk to have a small UA?

- Because they do not "train" as long as a full-term and end with no good muscles in the mouth
- What is the "training"

Fetal Life

- Fetal echography has brought a large amount of knowledge
- We train 2 important functions early during fetal development:
- .
- During fetal development there will be continuous "training" of sucking and swallowing under the control of neuronal networks that develops in the brain-stem and will constitute in part cranial nerve
- During fetal life, there will be continuous taining with progressive maturation overtime, of the coordination sucking, swallowing and protection of the airway that will abruptly be needed with birth and air-exchange
- Such fetal training is related to the **fetal-oral development and organization**

- **Fetal Oral development and organization**
- It begins near 2nd month of pregnancy
- Cells from neural crest, built 5 "modules" that will create the face and the oral cavity
- The internal part of the **oral cavity is a same as the skin** and has the same sensory receptors (pression, pain, light tact, temperature) as the skin
- It is near the 8th week GA that the **tongue move into the oral cavity**
- From the 3rd to the 5th month GA occurs an **organization** of normal oral functioning, critical for the development "suction-swallowing" that will be needed at birth. There are creation of brain-stem neuronal network aimed at suction and swallowing-very much coupled
- The passage of the tongue in its final position in the mouth, under the control of specific genes [particularly the family of the 39 Hox genes]
- Is a critical step for the development of the "oral functioning" of the fetus
- The **movement of the fetal tongue between 6th and 10th weeks GA** allow the closing [vertical, horizontal and transversal] of the primitive mouth (stomodeum)

- and the placement of the tongue below the palate, **changing a vertical orientation to an horizontal orientation,**
- simultaneously the cranial nerves come-up in the brain-stem [Genetic anomalies will be responsible for many syndromes including severe Pierre Robin syndrome].....
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- Once the tongue is in place, *the fetus can begin training for sucking and swallowing*
- **Contac**t between tongue-palate, lips-palate, start some sensory reflexes that will become more important with contact with hands, foot and near the 13-15th weeks
- there is the appearance of reflexes (Hoocker reflexes where the contact between lips (lips stimulation) leads **to opening of mouth, with protusion of tongue** –reflexes that are closely related to those seen at birth-
- Suction and swallow
- The two neuronal network are very closely related in the fetus with beginning by **suction.**
- **Swallowing** is associated with an esophageal reflex ie leading to movement of the bolus to the esophageus with a timing oro-pharyngeal and then esophageal
- These initial reflexes will be *functional immediately at birth*
- but
- between 6 and 12 month of life (post nataly) this initial reflex will persist but there will be development of an 'active" swallowing
- with development of a cortico-geniculum pathway that allows a voluntary swallowing impinging on the same initial neuronal network ie the primitive oral reflex is active through-out life
- The active swallowing is *a "praxia" which is associated with mastication* and it will be related to training with presence of inhibitory circuit

- So if the neuronal network "suction" is unchanged the neuronal network swallowing and mastication adds a secondary network
- With fetal echography it was shown that there is a **continuous sucking and swallowing activity beginning at the 18th week GA.**
- Starting the 20th week the fetus will ingest more and more amniotic fluid following this scheme
- Such activity lead to "reputation" movement of the mandible with movement of tongue (XII nerve) and contraction of external pterygoidian muscles (V motor)
- These muscles insert of the **growth centers of the mandibular condyle and activate growth of the ramus of the mandible**
- There is a relation between the sucking activity of the fetus and the mandibular growth
- **Suction and swallow**
- These 2 functions have to be fully active immediately at birth and are critical to development of oro-facial structures post birth
- If there is a disturbance or difficulty to perform, this has an impact:
- Abnormal development of orofacial structures
- ..... And secondary impact on size of UA
- ***....with increase risk of collapse of UA during sleep***
- **orofacial growth**
- Orofacial Growth from birth up to 13-15 years is dependent of
-
- + the intermaxillary growth center (synchondrosis)
- + the dento-alveolar growth center
- **If there is a problem with motility of the tongue?**
- What happens?
- Lingual frenulum

- The lingual frenulum, a small fold of mucous membrane that connects the middle of the sublingual face of the tongue to the floor of the mouth, **may interferes in the tongue movements and its functions if abnormally placed or short**.
- *Orofacial functions can be altered according to the degree of lingual frenulum alteration and limitation of tongue movements* *(Guilleminault etal ERJ2016)*
- An abnormal short lingual frenulum...
- Interferes with normal **tongue movements, and normal tongue functions**
- and impact on:
- + sucking
- +swallowing
- +chewing
- + speech
- If not treated...
- BUT the tongue is the largest muscle in the oral cavity [and for the space, of the entire body] and is the anterior border of the UA
- The presence of such anomaly is related to tongue apoptosis during embryologic development.
- Ankyloglossia is a congentital anomaly reported to be present in 4 to 5 % of general population
- (much higher frequency in our sample of children with SDB)
- May be inherited as an autosomal dominant trait (more common in men) , considered X linked
- May be associated with short *nasal* frenulum [impacting on alveolo-dental ligament]
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- **Direct impairment of growth centers** [c]

- +either intermaxillary cartilage (synchondrosis) a GROWTH center
- + or alveolo-dental Growth center
- Study of connective tissue diseases ie congenital cartilage disease
- Marfan Syndrome
- Ehlers Danlos Syndrome
- **Mutation affect the maxillary synchondrosis**
- Leading to abnormal maxillary development and appearance of complaints related to OSA/SDB: fatigue, disrupted sleep and daytime sleepiness and small oral cavity
- **Consequences**
- Abnormal oral facial growth:
- ---long narrow face
- ----high narrow hard palate
- .....abnormal oral facial anatomic growth with
- ...increase risk of UA collapsibility during sleep
- And... development of OSA that become more and more severe overtime
- **Investigation #4** (Lee etal 2015)
- **Impairment of the abnormal alveolo-dental growth region:**
- Genetically related
- Environmentally induced
- **Missing teeth**
- *Dental agenesis*
- *[either part of a syndromic presentation or isolated and limited to dental agenesis]*
- *are associated with changes in maxillary and/or mandibular growth.*
- *This abnormal growth is a risk-factor for small upper airway with secondary increased collapsibility during sleep*

- **Extraction of 2 or more permanent teeth during early childhood**
- Same evolution as for permanent teeth dental agenesis
- ... development of high and narrow hard palate and long and narrow face
- .... Development of OSA with progressive worsening of sleep disordered breathing over time
- **Investigation#5**
- **Impairment of nasal breathing.....**
- .....Abnormal increase in "nasal resistance*", as in the monkey model,* lead to mouth breathing and change in the "growth vector" of maxilla and mandible
- With absence of the normal muscles and cartilage stimulations
- **At birth** infants are obligatory nose breather and nasal breathing stimulate orofacial growth:
- +Enlarged inferior nasal turbinates
- +Deviated septum
- +Enlarged tonsils and adenoids
- .....are associated with these orofacial growth change
- Blockade of nose for any reason
- **leads to mouth breathing**
- **Mouth breathing impact on orofacial growth**
- Summary:,
  the Effects of Chronic Mouth breathing
- Alterations in Muscle Recruitment in the nasal and oral cavities leads to :
- **Change in posture**
- **Increase in nasal resistance**
- **Increased airway collapsibility**

- **Alterations in Facial Growth**
- **.....development of OSA**
- Interaction between airway resistance and oral-facial growth
- There can be an **anatomical problem** at birth (prematurity, genetic abnormality, skull base growth during fetal life, deviated septum, short frenulum etc) **associating an abnormal tongue posture, and mouth breathing leading to abnormal nasal resistance**
- There can be **an acquired abnormal nasal resistance in early life:** allergy, GE reflux, other inflammatory inducing problem leading to enlargement of nasal turbinates (occurring often before enlargement of lymphoid tissues) adeno-tonsils enlargement **will lead to abnormal tongue position and mouth breathing**
- **These factors increase the risks of UA collapsibility during sleep...and OSA**

What did we learn?

- *1-Impairment of oral facial growth related to genetic or environmental causes during childhood leads to development of OSA*
- 2-The development of symptoms associated with SDB may be slow and complaints related to this impairment may be seen only at late teen-age or adulthood
- But the anatomical changes may be noted much earlier
- *3-understanding what is behind the abnormal oral facial growth is crucial*
- 4- treatment must address the underlying cause... including the "nasal dis-use" during sleep(Lee et 2015)
- **Abnormal oral facial development and adulthood**
- Untreated abnormal development in childhood, leads to
- +Anatomic changes of the supports of the collapsible tube: the pharynx
- These changes in association with sleep increase risk of collapsibility of UA

- To this early in life untreated risk,
- other environmental factors will come-up
- There will be a *further worsening* with addition of impact of weight, soft tissues destruction, local inflammation, leukotriene infiltration
- **SDB is a disorder of repetitive vicious cycles and its avoidable**
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